Uremic Bleeding

By Kevin Stiles

Objectives

- To discuss normal hemostasis
- To the laboratory abnormalities of uremic hemostasis
- To discuss the pathophysiology of uremic hemostasis
- To discuss possible therapies

Historical Data

- Uremic Bleeding first described in the 18th Century
- Most bleeding episodes were mild (ecchymoses or purpura)
- Severe bleeding also noted
- Dialysis reduced the incidence of severe bleeding

Normal Hemostasis

- Primary Hemostasis - Platelet plug formation at injury site
- Secondary Hemostasis - Actions of the plasma coagulation system

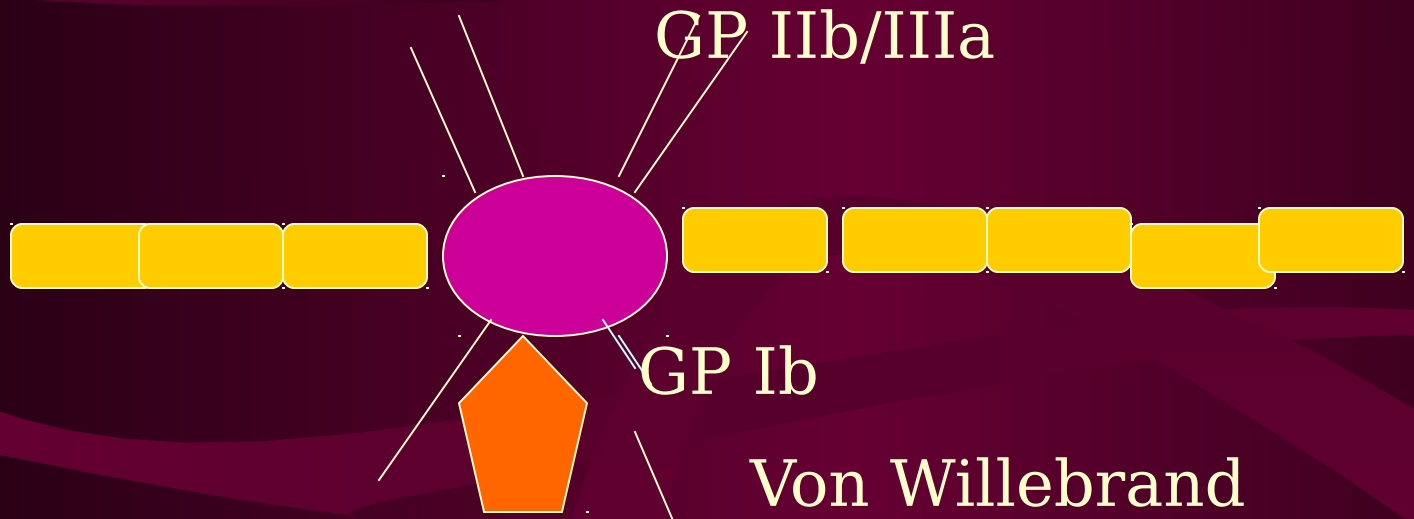
Adhesion

- Exposed vascular collagen binds to platelet receptors (GP Ia Gp Ib)
- Platelet is transformed
- GP IIbIIIa receptor changes configuration
- vwF stabilizes the interaction

Activation

- Produce thromboxane A2
- Transformation of shape
- Release of products from stored alpha, and dense granules
- Products include ADP, vwF, thromboxane A2, platelet factor #3, #4, and many others

Adhesion and Activation



ACTIVATION

Fibrinogen
(or vWF)

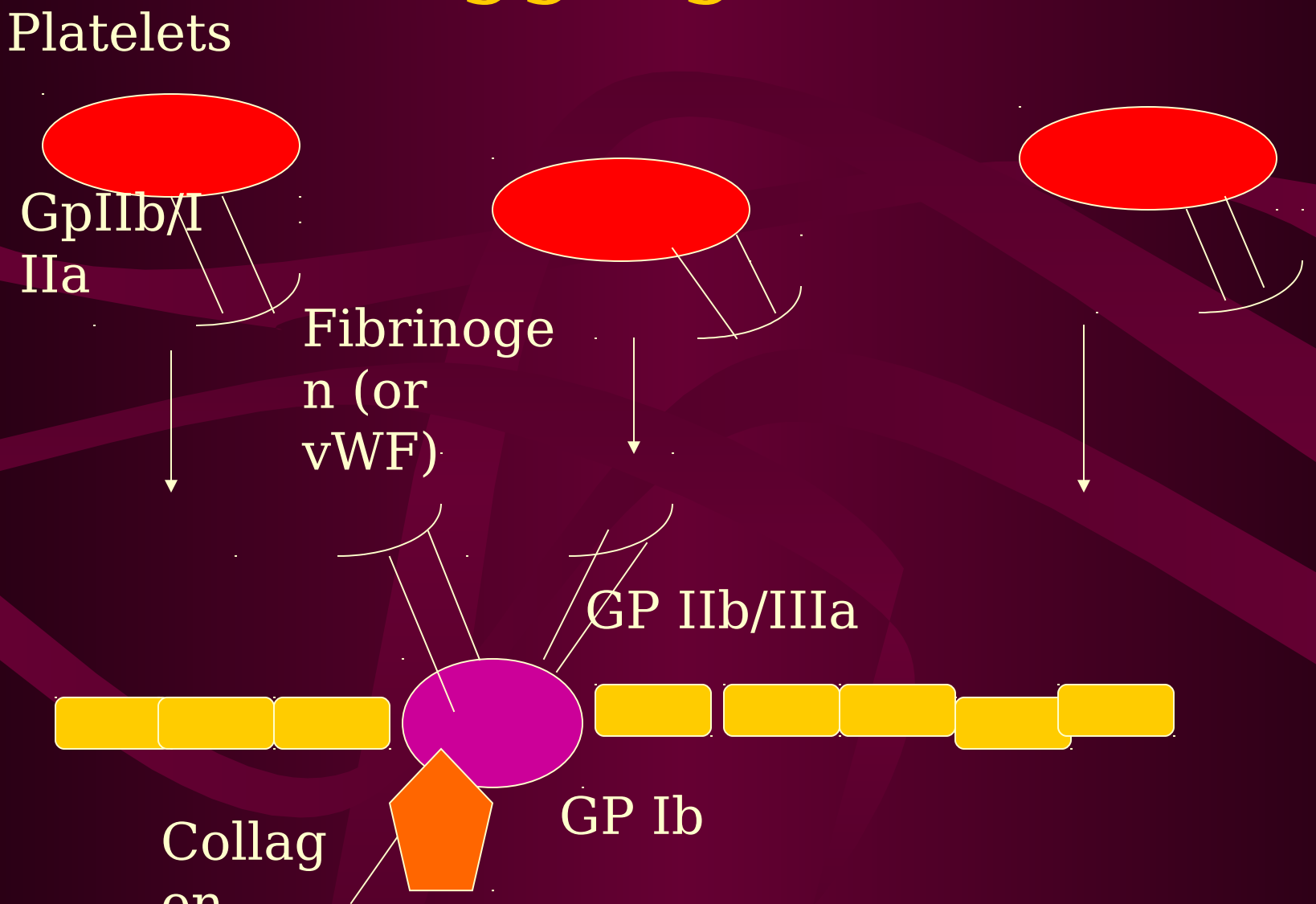
Amplification

- Phospholipases
- Protein Kinase
- cAMP

Aggregation

- ADP, collagen, epinephrine all are agonist
- Receptors transform configuration to allow aggregation
- Forms a platelet plug and fibrin network

Aggregation



Laboratory Evaluation

- Platelet count
- Impaired platelet adhesion(glass bead column retention), Baurngarther perfusion chamber
- Decreased platelet aggregation (Aggregometry, perfusion chamber method)

Laboratory Evaluation

- Impaired Release of ATP, Platelet factors 3/4
- Poor clot retraction
- Normal PT/PTT
- Increased bleeding time

Bleeding Time

- Laboratory test of primary hemostasis
- Lots of variability
- No evidence that bleeding time is useful in predicting bleeding in individual patient
- Doesn’t predict risk of hemorrhage
- Can’t predict efficacy of therapy

UREMIC HEMOSTATIC DEFECT

- Uremic retention products
- Chronic anemia
- Increased production of NO, PG
- Defective platelet-vwF binding
- Intrinsic defects
- Other factors

Uremic Retention Products

- Decrease in the episodes of bleeding since dialysis was instituted
- Several studies indicating at least some role in these products in uremic bleeding
- Association of these products and bleeding time

Small Molecules

- Phenol - decreased platelet factor 3
- GSA - decreased aggregation
- Urea - decreased glass bead retention
- Bleeding times increased with all small molecules
- Findings have not been reproduced consistently in follow-up studies

BUN/ Bleeding Times Eknoyan, NEJM 1969

- Noted bleeding time decreased after patient placed on low protein diet
- Noted bleeding time increased with induced azotemia

Other Products

- Middle molecules associated with defects in aggregation, activation, and intrinsic platlet storage pool defects
- PTH associated with inhibition of platelet aggregation, and secretion

BAUMGARTNER PERFUSION CHAMBER TESTS

- Normal Platelets in uremic plasma
- Decrease in adhesion compared to normal controls
- Increase in adhesion compared to uremic whole blood

Multifactorial Defects in Uremia

- Levels of small molecules don’t correlate with bleeding times
- Dialysis patient’s bleeding times never normalize
- Relation of duration/severity of uremia to bleeding problems is unknown
- Acute vs chronic renal failure differences unknown

Anemia

- Associated with decreased platelet transport
- At higher hematocrits, platelets are near the endothelial surface
- Endothelial surface is optimal site if injury occurs
- At lower hematocrits, the platelets are equally distributed in the vessel

Bleeding Times/Anemia

- Inverse relationship between bleeding time/hematocrit
- Hellen's 1961 study showed correlation in non-uremic patients
- Livio's Italian study showed correlation in uremic patients
- Fernandez 1986 study showed effect of transfusions on bleeding time

Other Factors associated with correction of anemia

- Improved glass bead retention with increased hematocrit
- Red cells also increase ADP, a platelet aggregate agonist
- Levels btwn, 26-30 % are thought to have optimal effect on bleeding time

Nitric Oxide

- Endothelial derived relaxing factor
- Uremic rat model showed association between nitric oxide precursors, and inhibitors and changes in bleeding times (Remuzzi JCI 1990)
- Increased levels of L-Arginine, increased level of cGMP, increased nitric oxide production in hemodialysis patients
- Remuzzi KI 1993

Prostaglandins

- PGI2 is potent inhibitor of platelet aggregation
- PGI2 increase associated with increased bleeding time
- Elevated levels of PGI2 in dialysis patients
- 6-Keto PGFIalpha (precursor) increased at injury site in dialysis patients

Defective vwF binding

- Synthesis of normal molecule in uremia
- Normal to increased levels in uremia
- Decreased levels of ristocetin cofactor activity
- ? Abnormal amount of high molecular weight vwF

Ordanes Study (Blood 1990)

- Used perfusion chamber study
- Found abnormal interaction of vwF with the GPIIbIIIa platelet receptor
- Found abnormal adhesion when vwF levels were adjusted in controls vs. uremics

Intrinsic Platelet Defects

- Abnormal GIIbIIIa receptor binding to vwF, and fibrinogen
- Abnormal metabolism of Thromboxane A2
- Abnormal membrane defects
- Abnormal platelet storage pool defects
- Abnormal intracellular calcium

Other Factors

- Massive bleeding episodes not typical of other acquired platelet abnormalities
- Bleeding time and other platelet function test abnormalities are mild compared to other disease
- Abnormal GI tracts
- Heparin

THERAPIES

- DDAVP
- Cyroprecipitate
- Estrogens
- Vascular Factor
- Nitric Oxide Synthesis Inhibitors
- Epogen/Transfusions
- Dialysis

DDAVP

- Associated with short-term correction of bleeding times
- Does not decrease bleeding times in all patients
- No controlled clinical studies indicating that it prevent excessive bleeding or stops active bleeding

Mode of Action

- Thought to be related to the stimulation release of vwF from endothelium, including a large proportion of large molecular weight vwF
- Improves ATP release
- Improves Serotonin Uptake
- Increase catecholamine release
- Decrease in Protein C inhibitors

Pharmacokinetics

- Dose used is 0.3 *u*g/kg IV or SC
- Intranasal dose is 3*u*g/kg
- Effect begins in 1 hour, lasts for 4-24 hours
- Tachyphalaxsis begins at 24-48 hours
- Treatment of choice when short-term prevention of bleeding is needed

Cryoprecipitate

- Enriched with factor VIII, fibrinogen, but contains almost all plasma ingredients
- Reykin (NEJM 1980) infused in uremic patient with rectal bleeding
- Uncontrolled study, found decrease in bleeding times, no clinical bleeding, and small/no increases in vwF
- Does not decrease bleeding times in all patients

Cryoprecipitate

- Mode of action is unknown
- Shortened bleeding times for 1-18 hours
- Indications: Emergent procedure
- Dosage : in studies used 10 units
- Associated with increased transmission of diseases

ESTROGENS

- Livio study (NEJM 1986) found significant decrease in bleeding times vs. placebo
- Seth study (Clinical Pharm 1988) uncontrolled study that showed cessation of clinical bleeding
- Marsh MB (Am J of Med 1990) showed decreased bleeding times, and cessation of bleeding with oral estrogens
- Transdermal Estrogens have also been found to decrease clinical bleeding and bleeding times (Schiff AJKD 1995)

MECHANISM

- Thought to be related to nitric oxide synthesis antagonism
- Remuzio (JCI 1991) Using Rat model showed L - Arginine reversed effects of strogen on bleeding times
- Also increases production of Thromboxane A2

DOSING

- 0.6mg/kg IV
- 50 mg/kg of oral estrogens
- Lower doses had no effect on bleeding time

VASCULAR FACTOR

- Mixture of low molecular weight peptides derived from bovine factor VII
- Mechanism of action thought to be binding of endothelial cells
- Shown to decrease bleeding times

Nitric Oxide inhibitors

- L-NNME
- Decreased bleeding times
- Associated with hypertension, acidosis
- Associated with birth defects in animal models

EPOGEN

- Shown to increase megakarocyte differentiation
- Increase in platelet adhesion independent of its effect on Hct.
- May increase platelet count
- Possible neutralizes uremic toxins

DIALYSIS

- Partially corrects bleeding time
- Slight increase in vWF
- Increase in Protein C
- PD vs HD